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We successfully engineered the CDM network labeled with fluorescent markers highlighting fibronectin - a protein of the extracellular matrix, and we also observed the dynamics of key components driving cell migration, such as the actin cytoskeleton and focal contacts. Our results reveal key differences between 2D and 3D cell migration. (i) We report new types of protrusions distinct from filopodia/lamellipodia reported on planar surfaces, which are driven by pressure. (ii) Our 3D network is deformed reversibly during migration and this allows the extraction of forces locally applied by cells. We correlate these local forces to the focal contacts dynamics, and our measures indicate a local pulling mechanism for forward cell motion and nucleus translocation. (iii) During migration, the nucleus local deformation by the cytoskeleton is needed to facilitate motion. These three phenomena - pressure-driven protrusions, local forces correlated to local focal contacts, and nucleus deformation driven by the cytoskeleton - are reproduced in microchannels matching cell dimensions. Altogether, our results show that mechanical confinement of cell and nucleus is the main cause for differences between 3D and 2D motions.

2292-Pos Board B429

Cells as Active Particles in Asymmetric Potentials: Motility under External Gradients

Jordi Comelles[1], David Caballero[2], Raphael Voituriez[3], Verónica Hortigüela[4], Viktoria Wollrab[1], Amélie L. Godeau[1], Josep Samitier[5], Elena Martínez[4], Daniel Riveline[1].
[1]Laboratory of Cell Physics ISIS/IGBMC, Université de Strasbourg, Strasbourg, France, [2]Laboratory of Cell Physics ISIS/IGBMC, Strasbourg, France, [3]7 Laboratoire de Physique Théorique de la Matière Condensée, Université Pierre et Marie Curie, Paris, France, [4]Biomimetic Systems for Cell Engineering, Institute for Bioengineering of Catalonia (IBEC), Barcelona, Spain, [5]Nanobioengineering group, Institute for Bioengineering of Catalonia (IBEC), Barcelona, Spain.

Cells undergo motion and this phenomenon is known to be important during development and in diseases such as cancer. In particular, cells can migrate *directionally*: this phenomenon drives tissue rearrangements that shape organs in embryos. Mechanical constraints and chemical gradients can contribute to set cell directions, but their respective roles remain poorly understood. Here we report a new assay where we tested the effects of external cues on single cell motion. We show, by using microfabricated topographical ratchet, that the nucleus dictates the directions of cell through mechanical guidance with its environment. We demonstrate that this direction can be tuned by combining this ratchet with a gradient of fibronectin adhesion. We report competitions and cooperations between both external cues depending on their relative orientations. We also quantitatively compare the measurements to a model treating cells as fluctuating particles trapped in a periodic asymmetric potential. We show that the nucleus is contributing to the strength of the trap whereas protrusions guided by the adhesive gradients add a constant tunable bias to the motion.

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Characterizing New Genes Regulating Cell-Substrate Adhesion to Discover Novel Regulatory Mechanisms of Cell Motility

Thomas J. Lampert, Peter N. Devreotes.
Cell Biology, Johns Hopkins School of Medicine, Baltimore, MD, USA.

The model organism Dictyostelium has greatly facilitated our understanding of the signal transduction and cytoskeletal pathways that govern cell motility. Cell-substrate adhesion is a target of many chemotaxis signaling events and it can be used to screen for cells that have defects in cell migration. In fact, cells lacking PTEN, a negative regulator of cellular extensions, is flatter and adheres strongly to the surface. This leads to reasoning that other regulators of migration would also effect adhesion, a screening method was devised and isolated overly adherent mutants from a pool of mutagenized cells. Restriction enzyme mediated insertion (REMI) mutagenized cells, comprising more than 50000 insertions, yielded about 100 mutated cell lines with the desired phenotypes. The mutation sites in 20 of the strains have been mapped and many of the phenotypes are similar to those of PTEN knockout cells. The extent of increased adhesion, cell motility, directed migration, cell shape, and new filamentous actin at the periphery are all parameters that have been examined in these new overly adhesive cell lines. The degree in which these parameters have been effected and the correlations between these changes is providing novel insights into the networks controlling cell motility. Many of these genes have human homologs with unknown functions. Therefore, the future study of this new group of regulators of adhesion and motility genes in Dictyostelium will not only advance the knowledge of cell migration in amoeboid cells but elucidate the functions of novel human genes with potential disease relevance.

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Evolutionarily Conserved Coupling of Adaptive and Excitable Networks Mediates Eukaryotic Chemotaxis

Chuan-Hsiang Huang[1], Ming Tang[1], Mingjie Wang[1], Changji Shi[1], Pablo A. Iglesias[2], Peter N. Devreotes[1].
[1]Cell Biology, Johns Hopkins University, Baltimore, MD, USA, [2]Electrical and Computer Engineering, Johns Hopkins University, Baltimore, MD, USA.

Numerous models have been proposed to explain the remarkable ability of chemotactic cells to sense and migrate toward extremely shallow chemoattractant gradients independently of the ambient concentration. We carried out experiments to distinguish the various models of gradient sensing in migrating cells. First, signaling activity was strongly suppressed toward the low side of cells in a gradient or following sudden removal of uniform chemoattractant. Second, signaling activities displayed a rapid shut off and, with stimulation of increasing duration, a slower adaptation during which responsiveness to subsequent test stimuli declined. Simulations of existing classes of models indicated that these observations can only be explained by the coupling between an adaptive module and an excitable network. Moreover, stimulation of cells lacking G-protein function suppresses downstream activities, while constitutive G-protein activation induced persistent responses. This indicates that chemoattractant sensing is mediated by a G-protein-dependent excitor and a G-protein-independent inhibitor forming an incoherent feedforward loop. The salient features of the coupling between adaptive and excitable networks were observed for the chemoattractants cAMP and folic acid in Dictyostelium as well as fMLP in human neutrophils, suggesting an evolutionarily conserved mechanism for eukaryotic chemotaxis.

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Cell Polarisation Driven by Substrate-Mediated Intracellular Interactions - Consequences for Migration and Chemotaxis

Marco Leoni, Pierre Sens.
ESPCI, Paris, France.

We study a generic model for the polarisation and motility of cells and biomimetic systems interacting with a viscous substrate, where traction forces generated by the cell are modelled by means of oscillating force multipoles at the cell/substrate interface. We find that symmetry breaking and cell polarisation naturally "emerge" from long-range mechanical interactions between oscillating units, mediated both by the intracellular medium and the substrate. However, the harnessing of cell polarisation for motility requires substrate-mediated interactions. Motility can be optimised by adapting the oscillation frequency to the relaxation time of the system, and maximal velocity is found when the substrate and cell viscosities match. Cellular noise can destroy mechanical coordination between force-generating elements within the cell, resulting in sudden changes of polarisation. The persistence of the cell's motion is found to depend on the substrate viscosity. Within such a model, chemotactic guidance of cell motion is obtained by directionally modulating the persistence of motion, rather than by modulating cell motility, in a way that resemble the run and tumble chemotaxis of bacteria.

2296-Pos Board B433

The Interplay between Cell Motility and Proteolysis in the Establishment of Brain Metastasis

Alexus Devine, Kandice Tanner.
National Cancer Institute, Bethesda, MD, USA.

Cells actively respond to the mechanical signals received from the extracellular matrix (ECM) milieu. Reciprocally, cells can also modify the chemical and physical composition of the ECM via coordinated motility and proteolysis. Tumor cells actively remodel their microenvironment during colonization of distant organs. Here, we sought to understand the mechanisms that allow for successful brain metastasis. Using 3D in vitro models, we determined that there are phenotypic differences between brain tropic cells and those that metastasize to other organs. We visualized the morphogenetic program of the cells to determine if a specific type of cell motility is necessary for successful colonization.

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Comparsion of Migration Pattern between Young and Senescent Mesenchymal Stem Cells in Time Lapse Microscopy

Ching-Fen Jiang[1], Shan-hui Hsu[2], Ka-Pei Tsai[1], Jia-Yin Li[1].
[1]Biomedical Engineering, I-Shou University, Kaohsiung, Taiwan, [2]Institute of Polymer Science and Engineering, National Taiwan University, Taipei, Taiwan.

Mesenchymal stem cells (MSCs) can differentiate into a variety of cell types, and thus are fundamental players in modern regenerative medicine. To maintain the viability and the potentials for self-renewal and multilineage differentiation of MSCs in vitro development remains a big challenge. Previous approaches found that when MSCs were cultured on chitosan membranes, they tended to aggregate and form a 3D spheroid; meanwhile, their differentiation efficiency was likely to